

WE CLAIM:

1. Pharmaceutical compositions of the peptides, secreted by the snake venom glands particularly *Bothrops Jararaca*, vasopeptidases inhibitors, Evasins, their analogues and derivatives characterized for comprising:

5 **a) oligopeptides of 5-13 amino acids**

<u>Formulas</u>	<u>Sequences</u>	<u>Nomenclature</u>
I	$\langle E^1 aa^2 aa^3 aa^4 P^5$	Evasin-5a, b,... n
II	$\langle E^1 aa^2 aa^3 aa^4 aa^5 P^6$	Evasin-6a, b,... n
III	$\langle E^1 aa^2 aa^3 aa^4 aa^5 P^6 P^7$	Evasin-7a, b,... n
10 IV	$\langle E^1 aa^2 aa^3 P^4 aa^5 aa^6 P^7 P^8$	Evasin-8a, b,... n
V	$\langle E^1 aa^2 aa^3 aa^4 aa^5 aa^6 aa^7 P^8 P^9$	Evasin-9a, b,... n
VI	$\langle E^1 aa^2 aa^3 aa^4 aa^5 P^6 aa^7 aa^8 P^9 P^{10}$	Evasin-10a, b,... n
VII	$\langle E^1 aa^2 aa^3 aa^4 aa^5 aa^6 P^7 aa^8 aa^9 P^{10} P^{11}$	Evasin-11a, b,... n
VIII	$\langle E^1 aa^2 aa^3 aa^4 aa^5 aa^6 aa^7 P^8 aa^9 aa^{10} P^{11} P^{12}$	Evasin-12a, b,... n
15 IX	$\langle E^1 aa^2 aa^3 aa^4 aa^5 aa^6 aa^7 aa^8 P^9 aa^{10} aa^{11} P^{12} P^{13}$	Evasin-13a, b,... n

where:

P is always proline. The others could be L- or D-amino acids and derivatives that are presented with the code of three and one letter

20	aspartic acid (Asp, D)	glutamic acid (Glu, AND)
	alanine (Ala, A)	arginine (Arg, R)
	asparagine (Asp, D)	phenylalanine (Phe, F)
	glycine (Gly, G)	glutamine (Gln, Q)
	histidine (His, H)	isoleucine (Ile, I)
	leucine (Leu, L)	lysine (Lys, K)
25	proline (Pro, P)	serine (Ser, S)
	tyrosine (Tyr, Y)	threonine (Thr, T)
	tryptophan (Trp, W)	valine (Val, V)
	aminobutyric acid (Abu)	aminoisobutyric acid (Aib)
	diaminobutanoic acid (Dab)	diaminopropionic acid (Dpr)
30	hexanoic acid (ϵ -Ahx)	isonipecotic acid (Isn)
	pyroglutamic acid (Pyr, <E)	
	tetrahydroisoquinoline-3-carboxylic acid (Tic)	

butyl-glycinecyclohexylalanine (Cha)

citrulline (Cit)

phenylglycine (Phg)

homoserine (Hse)

5 norvaline (Nva)

penicillinalanine (Pen)

tiethylalanine (Thi)

statin and derivatives (Sta)

hydroxyproline (Hyp)

norleucine (Nle)

ornitin (Orn)

sarcosine (Sar)

<E¹ pyroglutamic acid is the N-terminal amino acid;

10 aa² is an amino acid, typically W, S or K for formulas I and II, typically D for formula III and typically W, S, G or N for formulas IV to IX;

aa³ is typically W, P, F or G for formulas I to III and typically P, G, W or R for formulas IV to IX;

aa⁴ is an amino acid, typically P, A or R for formulas I to III and typically P, A, R or W for formulas IV to IX;

15 aa⁵ is an amino acid, typically R or I for formulas II and III and typically T, P, G, H, R, W or E for formulas IV to IX;

aa⁶ is an amino acid, typically Q, N, P, T, H, R or G for formulas V, VII, VIII and IX; it is usually I, A, T or Y for formula IV;

20 aa⁷ is an amino acid, typically N, Q, G or R for formulas VI, VIII and IX and usually I, A, T or Y for formula V;

aa⁸ is an amino acid, typically Q, P or G for formulas VII and IX; it is usually I, A, T or Y for formula VI;

aa⁹ is an amino acid, typically Q, N or G for formula VIII and usually I, A, T or Y for formula VII;

25 aa¹⁰ is an amino acid, typically Q and E for formula IX and usually I, A, T or Y for formula VIII;

aa¹¹ for formula IX is usually I, A, T or Y;

30 b) inclusion compounds of the Evasins, their analogues or derivatives in cyclodextrins or their derivatives, or associated or included in carriers and/or excipients acceptable pharmaceutically, alone or mixed or associated at least with another active pharmacological agent;

c) the Evasins, their analogues and derivatives included or not in cyclodextrins microencapsulated or not in controlled-release systems such as liposomes and biodegradable polymers and/or mixtures.

5 2. Pharmaceutical compounds of the Evasins, their analogues and derivatives characterized by utilizing the Evasins 7a, 10c, 11e, 12b their analogues and derivatives as a molecular model for development of drugs and/or formulations based on peptides compounds and/or non-peptide vasopeptidase inhibitors.

10 3. Pharmaceutical compositions of the Evasins, their analogues and derivatives characterized by utilizing the Evasins 7a, 10c, 11e, 12b, their analogues and derivatives as a molecular model for development of drugs and/ or formulations based in peptides compound and/or non-peptide ligand agonists and antagonists of the angiotensin converting enzyme bound to the membrane.

15 4. Compositions of the Evasins, their analogues and derivatives, except the Evasin-7a, according to the claims 1 and 2 characterized for presenting diferential inhibitory activity for the neutral endopeptidase (K_i in the micro molar range) and the angiotensin I converting enzyme (K_i in the nano molar range).

20 5. Pharmaceutical compositions of the Evasins, their analogues and derivatives according to the claims 1 and 2 characterized for presenting selective inhibitory activity for the C-terminal domain of the angiotensin I converting enzyme, being 50 a 400 fold more potent for the C – domain than for the N-domain.

6. Pharmaceutical compositions of the Evasins, their analogues and derivatives according to the 1 and 2 claims characterized for presenting selective binding to the C-terminal domain of the angiotensin I converting enzyme, being 50 a 400 fold more potent to the C domain than for the N-domain.

25 7. Pharmaceutical compositions to the Evasin-7a, their analogues and derivatives according to the claims 1 and 2 characterized for presenting similar inhibitory activity similar to the neutral endopptidase and the angiotensin I converting enzyme.

30 8. Utilization of the Evasins, 7a, 10c, 11e, 12b, their analogues and derivatives as a molecular model to the development of drugs and / or formulations based on peptide compounds and/or non-peptide compounds characterized for presenting vasodilator and/or vasoprotector activity.

- 5 9. Pharmaceutical compositions of the Evasins, their analogues and derivatives according to the claims 1 to 3 for application in the study and treatment of arterial hypertension and others cardiovascular diseases and their complications characterized by the use of inclusion compounds or association of the Evasins, their analogues and derivatives with the cyclodextrin and their derivatives, microencapsulated or not in controlled-release system such as example, liposome and the biodegradable polymers, and/or mixtures.
- 10 10. Pharmaceutical compositions of the Evasins, their analogues and derivatives according to the claims 1 to 6 useful for the study and treatment of acute myocardial infarction, left ventricular hypertrophy diabetic, vasculopathy, peripheral ischemia, angina, progressive heart failure after a myocardial infarction, atherosclerosis, tumors, diabetes melitus, sperm motility, blockade of spermatogenesis, nephropathies, sexual disfunction, gastrointestinal and gynecologic disorders, angiogenesis, hair loss, blood diseases, angioplasty (restenosis after-angioplasty, endoluminal protese) in warm-blood animals characterized by the use of inclusion compounds or association of the Evasins, their analogues and derivatives with cyclodextrins and their derivatives, microencapsulated or not in controlled-release systems such as the liposome and the biodegradable polymers and/or mixtures.
- 15 11. Pharmaceutical compositions according to claims 1 and 2 characterized by the mixture of the organic-aqueous solids or solutions of cyclodextrins or derivatives of cyclodextrins selected from the group containing alkyl, hydroxyalkyl, hydroxyalkyl, hydroxypropyl and acyl or cyclodextrins with cross-bonds or cyclodextrins polymers with solutions of Evasins, their analogues and derivatives at a molar ratio of 1:1 or 1:2.
- 20 12. Pharmaceutical compositions of the Evasins, their analogues and derivatives characterized by the use of the cyclodextrins, or others controlled-release systems including, liposomes, biodegradable polymers derivatives of biodegradable polymers or mixture of these systems.
- 25 13. Utilization of the Evasins as molecular models for the development of drugs and/or formulations with differential inhibitory activity for the neutral endopeptidase and the angiotensin I converting enzyme according to the claim 4 characterized for presenting a lower inhibitory activity for the neutral endopeptidase and consequently with a smaller possibility of incidence of collateral effects such as cough and angiodema.
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14. Pharmaceutical compositions for the study and treatment of arterial hypertension and others cardiovascular diseases and their complications characterized by the mixture of organic-aqueous or solid solutions of cyclodextrins or derivatives of cyclodextrin selected from the groups containing alquil, hydroxialquil, hydroxipropil and acyl or
5 cyclodextrins with crossed bonds or polymers of cyclodextrins, with aqueous or solids solutions of Evasins, their analogues and derivatives.
15. Pharmaceutical compositions to study and treatment of the acute myocardial infarction, left ventricular hypertrophy diabetic vasculopathy, peripheral ischemia, angina, progressive heart failure after a myocardial infarction, atherosclerosis, tumors, diabetes
10 melitus, sperm motility, blockade of spermatogenesis, nephropathies, sexual disfunction, gastrointestinal and gynecologic disorders, angiogenesis, hair loss, blood diseases, angioplasty (restenosis after-angioplasty, endoluminal protease) in warm-blood animals characterized by mixture of organic-aqueous or solid solutions of cyclodextrins or derivatives of cyclodextrins selected from the group containing alkyl, hydroxyalkyl,
15 hydroxypropyl and acyl or cyclodextrins with crossed bonds or polymers of cyclodextrins with aqueous or solid solutions of the Evasins, their analogues and derivatives.
16. Pharmaceutical compositions to be used as male contraceptive characterized by the mixture of organic-aqueous or solid solutions of cyclodextrins or derivatives of
20 cyclodextrins selected from the group containing alkyl, hydroxyalkil, hydroxypropyl and acyl or cyclodextrins with crossed bonds or polymers of cyclodextrins with aqueous or solid solutions of the Evasins, their analogues and derivatives.
17. Pharmaceutical compositions of the Evasins, their analogues and derivatives according to the claims 1,2 and 3, characterized by the increase of the biodisponibility of the cited
25 Evasins when included in cyclodextrins or their derivatives, or associated or included in carriers and/or excipients pharmaceutically acceptable, alone or mixed.
18. Pharmaceutical compositions of the Evasins, their analogues and derivatives according to the claims 1 and 2 characterized by the increase of the duration and/or efficacy of the
30 Evasins effect, their analogues and derivatives when included in cyclodextrins or their derivatives, or associated or included in carriers and/or excipients pharmaceutically acceptable, alone or mixed.

19. Oral pharmaceutical compositions of the Evasins, their analogues and derivatives, according to claims 1, 2, 3 and 4 to be used in the treatment of hypertensive emergency characterized by the use of the mixture with excipients pharmaceutically acceptable including water, saline solution, buffer solutions, Ringer solution, dextrose solution, Hank solution, Biocompatible saline solutions, containing or not polyethylene glycol.
20. Oral pharmaceutical compositions of the Evasins, its analogues and derivatives according to the claims 1 to 4 characterized by the increase of the bioavailability of the cited Evasins when included in cyclodextrins or their derivatives, or associated or included in carriers and/or excipients pharmaceutically acceptable, alone or mixed.
21. Pharmaceutical compositions oral of the Evasins, their analogues and derivatives according to the claims 1 and 2 characterized by the increase of the duration and/or efficacy of the Evasins effect, their analogues and derivatives when included in cyclodextrins or their derivatives, or associated or included in carriers and/or excipients pharmaceutically acceptable, alone or mixed.
22. Compositions and formulations for intramuscular, subcutaneous, topical, inhalatory (pulmonary, intranasal, intramouth) administration or as device that can be implanted or injected, of the Evasins, their analogues and derivatives according to the claims 1 to 4 characterized by the increase of the bioavailability of the cited Evasins, their analogues and derivatives when included in cyclodextrins or their derivatives, or associated or included in carriers and/or excipients pharmaceutically acceptable, alone or in mixture.
23. Compositions and formulations for intramuscular, subcutaneous, topical, inhalatory (pulmonary, intranasal, intramouth) administration or as device that can be implanted or injected, of the Evasins, their analogues and derivatives according to the claims 1 to 4 characterized by the increase of the bioavailability of the cited Evasins, their analogues and derivatives when included in cyclodextrins or their derivatives, or associated or included in carriers and/or excipients pharmaceutically acceptable, alone or in mixture or mixed or associated at least with another agent pharmacologically active microencapsulated or not in controlled-release systems such as liposome and the biodegradable polymers and/or mixtures.
24. Compositions and formulations for intramuscular, subcutaneous, topical, inhalatory (pulmonary, intranasal, intramouth) administration and as device that can be implanted or injected, of the Evasins, their analogues or derivatives according to the claims 1 to 4

characterized by the increase of the duration and/or efficacy of the cited Evasins, their analogues or derivatives when included in cyclodextrins or their derivatives, or associated or included in carriers and/or excipients pharmaceutically acceptable, alone or mixed .

- 5 25. Compositions and formulations for intramuscular, subcutaneous, topic, inhalatory (pulmonary, intranasal, intramouth) administration or as device that can be implated or injected, of the Evasins, their analogues and derivatives used in the study and treatment of the arterial hypertension and others cardiovascular diseases and their complications according to the claims 1 to 4, characterized by the use of the Evasins their analogues and derivatives when included in cyclodextrins or their derivatives, or associated or
10 included in carriers and/or excipients pharmaceutically acceptable, alone or in mixture associated, at least, with an additional pharmacologically active agent microencapsulated or not in controlled-release systems such as liposomes and biodegradable polymers and/or mixtures thereof.
- 15 26. Compositions and formulations for intramuscular, subcutaneous, topic, inhalatory (pulmonary, intranasal, intramouth) administration or as device that can be implanted or injected, of the Evasins, their analogues and derivatives used in the study and treatment of the acute myocardial infarction, left ventricular hypertrophy, diabetic vasculopathy, peripheral ischemia, angina, progressive heart failure after a myocardial infarction, atherosclerosis, tumors, diabetes melitus, sperm motility, blockade of spermatogenesis, nephropathies, sexual disfunction, gastrointestinal and gynecologic disorders, angiogenesis, hair loss, blood diseases, angioplasty (restenosis after-angioplasty, endoluminal protese) in warm-blood animals according to the claims 1 to 4 characterized by the use of the Evasins their analogues and derivatives when included in cyclodextrins
20 or their derivatives, or associated or included in carriers and/or excipients pharmaceutically acceptable, alone or in mixture associated, at least, with an additional pharmacologically active agent microencapsulated or not in controlled-release systems such as liposomes and biodegradable polymers and/or mixtures, thereof.
- 25 27. Pharmaceutical compositions for intramuscular, subcutaneous, topic, inhalatory (pulmonary, intranasal, intramouth) administration or as device that can be implated or injected, of the Evasins, their analogues and derivatives according to the claims 1 and 2 characterized by the increase of the biodisponibility of the cited Evasins, their analogues
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and derivatives when included in cyclodextrins or their derivatives, or associated or included in carriers and/or excipients pharmaceutically acceptable, alone or mixed or associated at least with an additional pharmacologically active agent microencapsulated or not in controlled-release systems such as liposome and the biodegradable polymers and/or mixtures.

28. Pharmaceutical compositions and formulations for intramuscular, subcutaneous, topic, inhalatory (pulmonary, intranasal, intramouth) administration or as device that can be implanted or injected, of the Evasins, their analogues and derivatives according to the claims 1 to 4, characterized by the increase of the duration and/or efficacy of the Evasins effect, their analogues and derivatives when included in cyclodextrins or their derivatives, or associated or included in carriers and/or excipients pharmaceutically acceptable, alone or mixed.
29. Pharmaceutical compositions, intramuscular, intravenous, subcutaneous, topic, inhalation (pulmonary, intranasal, intramouth) or as device that can be implanted or injected, of the Evasins, their analogues structural and conformational according to the claims 1 to 4 characterized by the increase of the duration and/or efficacy of the Evasins, their analogues and derivatives effect when included in cyclodextrins or their derivatives, or associated or included in carriers and/or excipients pharmaceutically acceptable, alone or mixed, at least, with an additional pharmacologically active agent and/or microencapsulated or not in controlled-release systems such as liposomes and biodegradable polymers and/or mixtures, thereof.
30. Pharmaceutical compositions for intramuscular, intravenous, subcutaneous, topic, inhalation (pulmonary, intranasal, intramouth) administration or as device that can be implanted or injected, of the Evasins, their analogues and derivatives used in the study and treatment of arterial hypertension and others cardiovascular and their complications according to the claims 1 to 4, characterized by the use of the Evasins their analogues and derivatives when included in cyclodextrins or their derivatives, or associated or included in carriers and/or excipients pharmaceutically acceptable, alone or in mixture associated at least with an additional pharmacologically active agent microencapsulated or not in controlled-release systems such as the liposomes and biodegradable polymers and/or mixtures, thereof.

31. Pharmaceutical compositions for intramuscular, intravenous, subcutaneous, topic, inhalation (pulmonary, intranasal, intramouth) or as device that can be implanted or injected, of the Evasins, their analogues and derivatives used in the study and treatment of the acute myocardial infarction, stroke, left ventricular hypertrophy, diabetic vasculopathy, peripheral ischemia, angina, progressive heart failure after a myocardial infarction, atherosclerosis, tumors, diabetes melitus, sperm motility, blockade spermatogenesis, nephropathies, sexual impotence, gastrointestinal and gynecologic disorders, angiogenesis, hair loss, blood diseases, angioplasty (restenosis after-angioplasty, endoluminal protese) in warm-blood animals according to the claims 1 to 4 characterized by the use of the Evasins their analogues and derivatives when included in cyclodextrins or their derivatives, or associated or included in carriers and/or excipients pharmaceutically acceptable, alone or in mixture associated, at least, with an additional pharmacologically active agent microencapsulated or not in controlled-release systems such as the liposomes and biodegradable polymers and/or mixtures, thereof.

15	ID nº	<u>Nomenclatura</u>	<u>Seqüência</u>
	ID 1	EVASIN-5a	<EKWAP
	ID 2	EVASIN-5b	<EWPRP
	ID 3	EVASIN-5c	<EKFAP
	ID 4	EVASIN-6a	<ESWPGP
20	ID 5	EVASIN-7a	<EDGPIPP
	ID 6	EVASIN-9a	<EWPRPQIPP
	ID 7	EVASIN-9b	<ESWPGNIPP
	ID 8	EVASIN-10a	<ESWPGPNIPP
	ID 9	EVASIN-10b	<ENWPRPQIPP
25	ID 10	EVASIN-10c	<ENWPHPQIPP
	ID 11	EVASIN-10d	<ESWPEPNIPP
	ID 12	EVASIN-11a	<EWPRPTPQIPP
	ID 13	EVASIN-11b	<EGRAPGPPIPP
	ID 14	EVASIN-11c	<EGRAPHPPIPP
30	ID 15	EVASIN-11d	<EGRPPGPPIPP
	ID 16	EVASIN-11e	<EARPPHPPIPP
	ID 17	EVASIN-12a	<EGWAWPRPQIPP

ID 18	EVASIN-12b	<EWGRPPGPPIPP
ID 19	EVASIN-13a	<EGGWPRPGPEIPP
ID 20	EVASIN-13b	<EGGLPRPGPEIPP
ID 21	EVASIN-13c	<EGGWPRPGPQIPP